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Clinical Trial Regulation
– an Update –
Outcomes of Pilot Procedures in BfArM

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Agenda

1. From Directive to Regulation: key changes and principles of the CTR
2. Update on the status of the CTR
3. The German Pilot Project
   - Principles of the Project
   - Outcomes
   - Lessons learned
4. Conclusion

1. From Directive to Regulation

Key changes and principles of the Clinical Trial Regulation (CTR)

Clinical Trials in the EU

Before May 2004

National rules only, no harmonisation within the EU

- Paper based submission
- National competent authorities (NCA) not in all Member States (MS) involved

Directive 2001/20/EC
(since May 2004)
First harmonisation step, but still many national specificities

- E-application form but otherwise paper based submission
- Both, NCA + ethics committee (EC) involved, but work usually independently of each other

Regulation (EU) No. 536/2014
(2022)
Full harmonisation and joint assessment of multi-state trials

- E-submission through EU portal (CTIS) for all MS
- Joint assessment of all Member States concerned (MSC)

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Current situation in Germany based on the principles of Directive 2001/20/EC

- Each clinical trial has to be **authorised by the competent NCA (BfArM/PEI)**
- Each clinical trial requires a **favourable opinion issued by the EC** concerned for the coordinating investigator
  - In Germany: 50 ECs, located at medical faculties and State medical associations
- Both bodies review the clinical trial application (CTA) and the essential documents submitted by the sponsor independently of each other
  - Different opinions on a trial protocol could lead to “ping pong” amendments
- For multicentre trials, each trial site must additionally obtain a favourable opinion on its suitability for the particular trial from the local ECs
- Multi-state trials require a new CT authorisation in each MS
- Overall: CT authorisation implies highly bureaucratic burden

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The CTR

Motivation & Objectives

- To stay with the fundamental GCP principles but to implement a more risk based approach to reduce unnecessary bureaucratic burden
- Further harmonisation of clinical trials in the EU through a directly applicable EU Regulation instead of a Directive
- To simplify the clinical trial application (CTA) submission process by use of modern IT technologies
  - EU portal +EU database = clinical trial information system (CTIS)
- To implement a joint/coordinated review for multi-state trials
- To enhance transparency on clinical trials and their results
- Overall: To foster innovation and keep the EU attractive for research

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Key changes and principles of the CTR

- Segmentation of the CTA dossier and the assessment report into two parts
  - **Part I** identical for all **Member States concerned (MSC)**: protocol, IMP dossiers, investigator's brochures …
  - **Part II** covers the national concerns in each MSC: informed consent, damage compensation …
- **Joint assessment of Part I** by all MSC under coordination of a **Reporting Member State (RMS)**
  - RMS manages communication and drafts the initial assessment report for the joint assessment by all MSC
  - RMS consolidates final assessment report and concludes decision on Part I (binding for all MSC)
- Development of an **EU clinical trial information system (CTIS)** for
  - Electronic submission of the CTA and related documents to all MSC without need of (electronic) signatures
  - Secure communication between sponsor, RMS and MSC
  - Content of CTIS is publicly accessible except some confidential information

The CTR
NCA and EC interaction

- The CTR does not specify whether and how ECs or NCAs are to be involved in the CT authorisation process
- Each Member State has to provide a **single decision** on a CTA in a set time limit
- Only requirement: national assessment team must have the necessary competence at its disposal and should include layperson(s)
  - Most Member States will involve both EC and NCA in the assessment (Germany too)
- Although the CTR requires that MSC must follow the decision of the RMS on part I, the CTR allows MS to implement a right of Veto for ethics committees in principle (not foreseen in all Member States)

The CTR

New definitions on clinical investigations

- **Clinical study:** Investigation on medicinal products with regard to efficacy, safety or pharmacokinetics to ascertain their safety and/or efficacy
- **Clinical trial:** A clinical study where treatment assignment is decided in advance and is in contrast to the normal clinical practise, prescription and study inclusion is taken together, or diagnostic or monitoring in addition to normal clinical practise are applied
- **Low-intervention trial:** A clinical trial where
  - All IMPs (except placebo) are authorised and used in-label or in an evidence-based off-label use
  - The additional procedures have only minimal additional risks and burden compared to normal clinical practise
- **Cluster trial:** A low-intervention clinical trial that randomizes trials sites rather than individual trial subjects (not foreseen in all Member States)
- **Non-interventional study (NIS):** A clinical study other than a clinical trial

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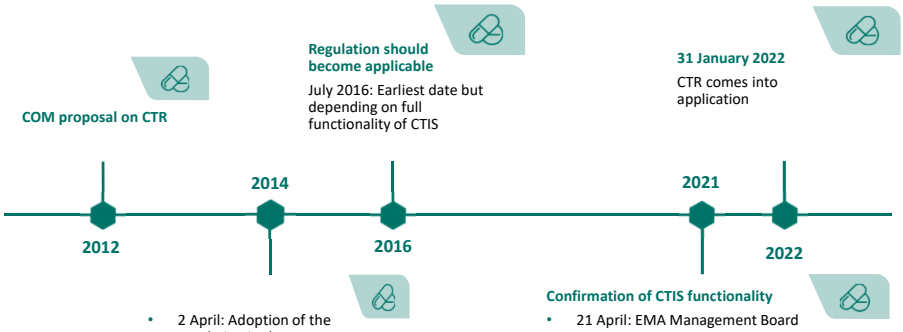
2. Update on the status of the CTR

One decade of development and current situation

The CTR

Status of implementation and coming into application



- 2 April: Adoption of the regulation in the European Parliament
- 14 April: Adoption of the Regulation by the Council of the European Union
- 16 June: Regulation published in the OJ of the EU

Confirmation of CTIS functionality

- 21 April: EMA Management Board confirmed full functionality of CTIS based on independent audit report
- 31 July: Publication of the Notice of the COM in the OJ on the compliance of CTIS with the requirements referred to in Article 82 (2)

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The CTR

Legal implementation in Germany

- Although the CTR is direct applicable in all Member States, some elements of the CTR require **national implementations**, e.g.
  - Rules of procedures on how a CTA is assessed nationally and which national body issues the final decision
  - Rules for assignment of the EC concerned (implemented by a **EC business distribution plan**)
  - Rules for damage compensation, inclusion of adults not capable of giving informed consent …
- The **German Medicinal Products Act (AMG)** has been prepared with the 4th AMG Amendment Act ("4. AMGuaÄndG") to implement adapted rules for clinical trials
  - Sections 41a, 41b and 41c have already entered into force in December **2016** (registration of ECs)
  - A new **Clinical Trial Assessment Procedure Ordinance (KPBV)** has been published in **July 2017**
  - Further AMG modification will come into force **on 31 January 2022 -** when the Regulation becomes applicable
  - Fee ordinances for both NCAs not yet published

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3. The German Pilot Project
Principles of the Project

Soon after publication of the CTR it became obvious that a collaboration between ECs and NCAs would be necessary as the German ministry of health intended to involve NCAs **and** ECs in the assessment of **part I** of the CTA, while part II should be assessed exclusively by the ECs

On initiative of BfArM and in close cooperation with the German *Association of Medical Ethics Committees* the Pilot Project was designed

Intention and principles

Process design for a joint part I assessment by EC and NCA

A pure CTR simulation with dummy CTAs would be little interest for all parties involved
Therefore: Boot/training camp approach with incentives

- Simulation of the CTR processes with current (active) CTAs, no dummies!
- Same* processes as defined in the CTR
  - But fully compliant with current legal requirements to ensure legally correct decisions
- Deadlines* of the CTR for NCAs, ECs and sponsors
  - If deadline exceeded: Fallback to standard procedures according to AMG/GCP-V
- Therefore, only mono-national CTAs could be submitted under the Pilot Project
- Incentives for sponsors: Shorter deadlines due to parallel assessment by NCA & EC
- Incentives for NCAs/ECs: Learning and gaining experience

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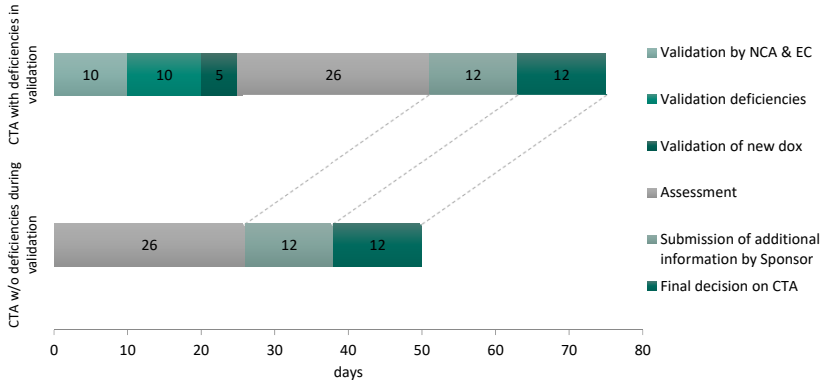
*as far as legally possible at the moment

Deadlines



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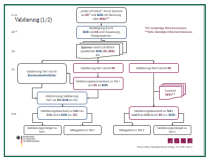
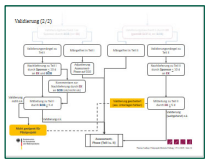
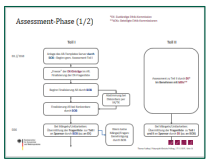
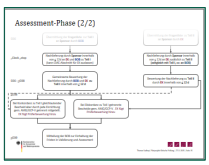
Process development

- "Letter of intend" to harmonise the start of the procedure between EC, NCA and sponsor
- Electronic CTA submission by EudraLink
- All procedure-related communication between sponsor and NCA/EC exclusively by email
- Joint preparation of the assessment report based on the VHP AR template
- Secure communication between EC and NCA and secure access to the assessment report provided by a Sharepoint® platform hosted by BfArM
- Monthly video conferences between BfArM, PEI and participating ECs
- Submission guideline for sponsors in German and English language
- First CTA submission after a 9 months planning in November 2015









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2. The German Pilot Project Outcomes

Outcomes and conclusions

Some Metrics
(as of end of August 2021)

	n
Number of CTAs submitted (BfArM/PEI)	348 (345/3)
CTAs directly approved without RFI*	18
CTAs approved with RFI*	223
CTAs rejected within the procedure	10
Procedures aborted/withdrawn	81
CTAs under review	10
Divergent decisions between EC and NCA	8
CTAs scheduled but not launched (letter of intend)	3

*RFI: request for additional information during assessment phase

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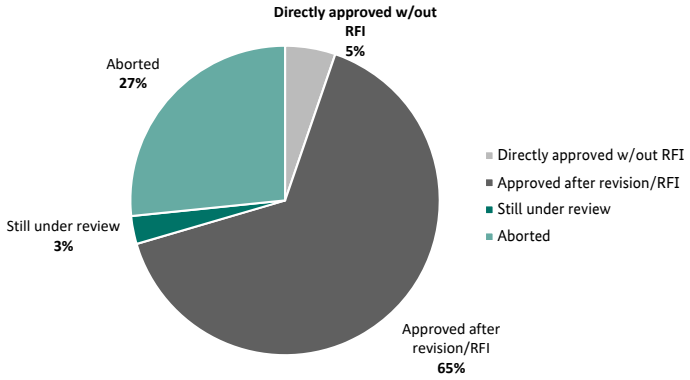
Metrics of 322 approved CTAs



RFI: request for additional information during assessment phase

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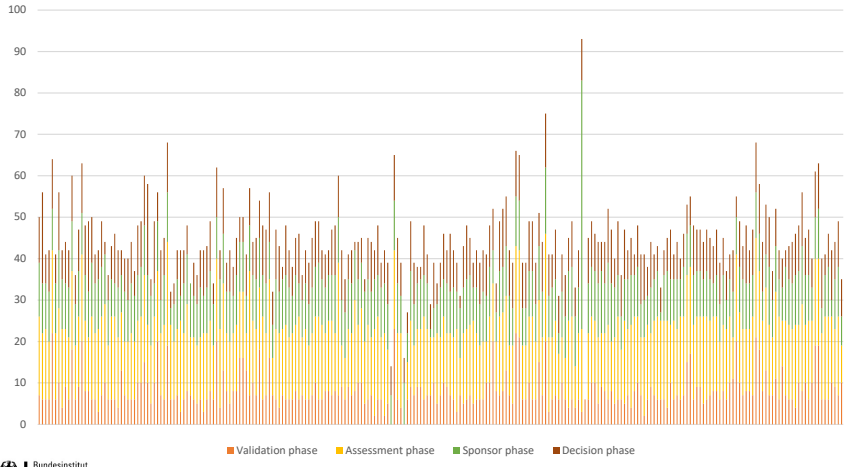
Duration of the different phases



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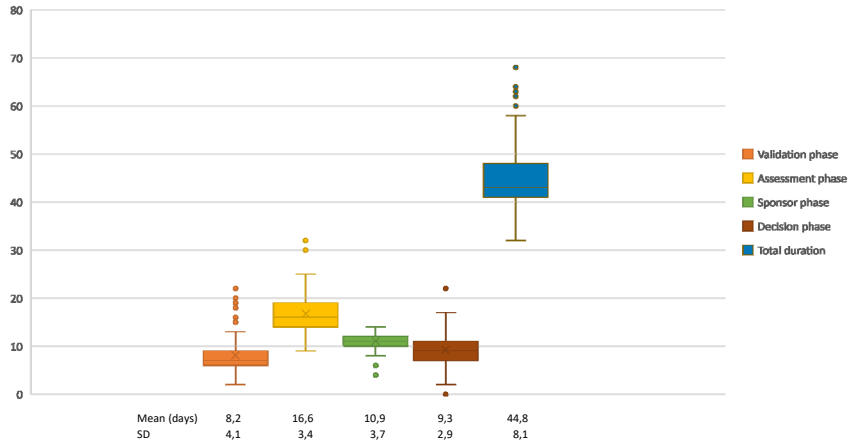
Duration of the different phases



	Validation phase	Assessment phase	Sponsor phase	Decision phase	Total duration
Mean (days)	8,2	16,6	10,9	9,3	44,8
SD	4,1	3,4	3,7	2,9	8,1

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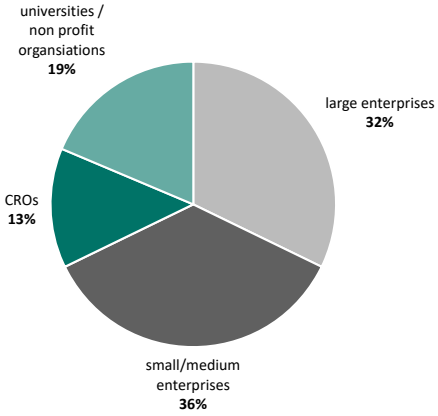
Who took part?

Applicants
Type of organisations



- 59 unique applicants in the pilot project
- Most applicants could be characterised as pharmaceutical companies (68%)

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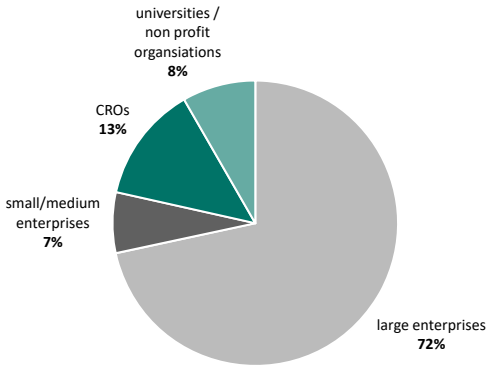
Applicants
Number of CTAs



- The vast majority of CTAs were submitted be large pharmaceutical companies

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Top 10 applicants

Applicants	% CTAs
Large Swiss pharmaceutical company	21 %
Large German pharmaceutical company	19 %
Large German pharmaceutical company	17 %
German CRO (specialised)	4 %
Large French pharmaceutical Company	3 %
German CRO	3 %
German university	3 %
Large American pharmaceutical company	3 %
International CRO	3 %
Large Danish pharmaceutical company	2 %

- 57% of the CTAs were submitted by only 3 large companies:
  - 1 from Switzerland
  - 2 from Germany

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Lessons learned

Lessons learned

- The joint CTA assessment by EC and NCA accelerated the review process and significantly shortened the overall procedure time A1
- The joint assessment increased the number of requests for additional information
- 26% of the CTAs were either withdrawn/aborted or rejected
- The Pilot Projects was mainly used by large companies for mono-national trials
- Unfortunately, the CTAs were not evenly distributed between the individual ECs
  - 49% of all CTAs were in the scope of only 3 ECs
  - Many ECs received no CTA or only one or two, so there was no training effect for them
- Nevertheless, it was considered helpful by all stakeholders

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Messages “to go”

1. It works!

- CTR deadlines can be met by all stakeholders,
- but all stakeholders had to learn and to set up clear processes to meet the tight deadlines!

2. Direct cooperation and communication is helpful!

- Ethics committees and BfArM highly appreciate the direct cooperation and communication on individual CTAs
- PP supported more consistent assessments by all registered ethics committees

3. But: All good things come to an end!

- Now that the start date of the CTR has been set to 31 January 2022, the German Pilot Project will end in September 2021

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A1 Autor; 13.09.2021

Thank you very much for attention

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